IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF MISSOURI

VITTI LABS, LLC,
834 West Kansas Street, Suite C
Liberty, MO 64068

Plaintiff,

v.

U.S. FOOD AND DRUG ADMINISTRATION and ROBERT CALIFF, M.D., in his official capacity as Commissioner of the Food and Drug Administration,
10903 New Hampshire Ave.
Silver Spring, MD 20993

and

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, and XAVIER BECERRA, in his official capacity as Secretary of Health and Human Services,
200 Independence Ave., S.W.
Washington, DC 20201

Defendants.

Case No. _____

COMPLAINT

1. For over 20 years, tissue banks like Plaintiff Vitti Labs, LLC ("Vitti Labs") have provided much needed human tissue products to healthcare professionals and their patients. These products are manufactured from human tissues (e.g., umbilical cord) that are then transferred into a human recipient.

2. Since 2001, this has been successfully accomplished through appropriate oversight by Defendant U.S. Food and Drug Administration ("FDA") without unnecessary regulatory restrictions placed on manufacturers who are investing substantial time and resources

into valuable research and development. The healthcare industry now has ready access to numerous affordable tissue products that can be used safely to promote quality of life.

3. With Vitti Labs, however, FDA has abandoned this approach. Vitti Labs recently developed a product branded CORDGRAFT which is derived from bio-ethically donated umbilical cord. It is well-established in the scientific community that tissue components of the umbilical cord protect the vein and arteries (i.e., conduit material) found in the cord by acting as a barrier, cushion, or cover. Vitti Labs preserves these characteristics when it cuts the tissue into square pieces that Vitti Labs refers to as "sheets." These sheets can then be used by medical practitioners to cover, cushion, and protect exposed structures like nerves and tendons during surgery. For instance, Vitti Labs intends for practitioners to use the sheets to wrap exposed structures such as nerves and tendons.

4. However, in responding to a formal request (called a Request for Designation or "RFD") submitted by Vitti Labs, FDA stated that CORDGRAFT is subject to regulation under more burdensome requirements applicable to "biologic" products covered by Section 351 of the Public Health Service Act ("PHS Act"). 42 U.S.C. § 262. FDA concluded that Vitti Labs may not avail itself of more reasonable regulations under Section 361 of the PHS Act which governs tissue products similar to CORDGRAFT. 42 U.S.C. § 264. FDA reaffirmed its decision in response to a Request for Reconsideration ("RFR") submitted by Vitti Labs.

5. FDA's responses were based on a single step taken by Vitti Labs when processing the tissue – i.e., cutting the umbilical cord lengthwise so that it lays flat on the processing station before it is further fashioned into sheets. According to FDA, this single cut somehow wholly transforms the umbilical cord, which FDA has long recognized as consisting of structural tissue that serves as a barrier, cushion, or cover, into something completely different – a "biologic"

product subject to extensive regulatory and premarket authorization requirements. FDA never adequately justifies how the umbilical cord tissue completely loses its ability to serve as a barrier, cushion, or cover based on this one step.

6. Vitti Labs therefore brings this action requesting this Court vacate and remand FDA's responses to the RFD and RFR. As demonstrated in this Complaint, FDA violated the Administrative Procedure Act ("APA") by, *inter alia*, failing to: (i) adhere to the plain language of FDA's own regulations implementing Section 361 or any reasonable interpretation thereof; (ii) follow its own public guidance regarding what types of products qualify under Section 361; (iii) provide a reasoned explanation for its decision, including its departure from longstanding policies regarding Section 361 products; (iv) consider all relevant evidence demonstrating CORDGRAFT should be regulated solely as a Section 361 product and not as a biologic; and (v) treat CORDGRAFT in a manner similar to other tissue products that qualify under Section 361.

PARTIES

7. Plaintiff Vitti Labs, LLC ("Vitti Labs") is a Missouri limited liability company with its principal place of business in Liberty, Missouri. The company is located at 834 West Kansas Street, Suite C, Liberty, Missouri.

8. Defendant U.S. Food and Drug Administration ("FDA") is an agency of the United States government and a part of the U.S. Department of Health and Human Services ("HHS"). FDA has been delegated authority to administer the federal Food, Drug and Cosmetic Act ("FDCA") and the Public Health Service Act ("PHS Act"). FDA is headquartered at 10903 New Hampshire Ave., Silver Spring, Maryland.

9. Defendant Department of Health and Human Services is an agency of the United States government. HHS is headquartered at 200 Independence Ave., S.W., Washington, D.C.

10. Defendant Robert Califf, M.D. is sued in his official capacity as the FDA Commissioner.

11. Defendant Xavier Becerra is sued in his official capacity as the HHS Secretary.

JURISDICTION AND VENUE

12. This suit arises under the Administrative Procedure Act ("APA"), 5 U.S.C. §§ 500 *et seq.*, the FDCA, 21 U.S.C. §§ 301 *et seq.*, and the PHS Act, 42 U.S.C. §§ 201 *et seq*.

13. This Court has jurisdiction under 28 U.S.C. §§ 1331 and 2201-02.

14. Judicial review of final agency action under the APA is authorized at 5 U.S.C. §§ 701 *et seq.* FDA's decisions on the RFD/RFR constitute final agency action that is reviewable under the APA. *See*, *e.g.*, *Genus Med. Techs. LLC v. FDA*, 994 F.3d 631, 636 (D.C. Cir. 2021).

15. Venue is proper under 28 U.S.C. § 1391(e). Vitti Labs is headquartered in Liberty, Missouri, which is within this district.

FACTUAL BACKGROUND

PHS Act's Section 361 Regulatory Framework

16. Section 361 of the Public Health Service Act ("PHS Act") authorizes the FDA to make and enforce regulations "necessary to prevent the introduction, transmission, or spread of communicable diseases" from foreign countries into the United States or between states. 42 U.S.C. § 264.

17. FDA used this authority to establish a framework at 21 C.F.R. Part 1271 for regulating Human Cells, Tissues, and Cellular and Tissue-Based Products ("HCT/Ps") like the CORDGRAFT made by Vitti Labs. The regulations were promulgated by final rule and published in the Federal Register on January 19, 2001. Human Cells, Tissues, and Cellular and

Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5447 (Jan 19, 2001). The basic HCT/P framework has been in place since the HCT/P regulations were adopted.

18. The HCT/P regulations establish a tiered, risk-based approach that recognizes HCT/P products may pose different degrees of risk as to communicable diseases. The "goal of the new approach is to improve protection of public health without imposing unnecessary restrictions on research, development, or the availability of new products." *Id.* In other words, the "regulation of different types of [HCT/Ps] will be commensurate with the public health risks presented." *Id.*; *see also id.* at 5448 (explaining that under this approach, FDA will "exert only the type of government regulation necessary to protect the public health").

19. The regulations define **"HCT/Ps"** to mean "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, [and] cornea." 21 C.F.R. § 1271.3(d)(2).

20. HCT/Ps that are regulated solely under Section 361 do not require further evaluation as "drugs" under Section 505 of the FDCA or as "biologic" products under Section 351 of the PHS Act. 21 U.S.C. § 355; 42 U.S.C. § 262. In other words, HCT/Ps that qualify under Section 361 do not require premarket review and approval. In contrast, to market a biologic product for example, a manufacturer must obtain a valid biologics license, and during the development stage when conducting human clinical trials, it must also have an Investigational New Drug ("IND") application in effect. 42 U.S.C. § 262(a)(1); 21 U.S.C. § 355(i)*; see* 66 Fed. Reg. at 5449 (explaining that HCT/Ps that meet certain criteria do not need to comply with additional regulations governing drugs or biologics).

21. To be regulated exclusively under Section 361, the HCT/P tissues must satisfy a list of requirements at 21 C.F.R. § 1271.10. There are two requirements in particular that are relevant to this Complaint. First, the tissues used to manufacture the HCT/Ps must have been only "minimally manipulated." Second, the HCT/Ps themselves must be "intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent." 21 C.F.R. §§ 1271.10(a)(1)-(2).[1]

22. The HCT/P regulations define "**Minimal manipulation**" with regard to "structural tissue" (as opposed to human cells), as "*processing* that does not alter the *original relevant characteristics* of the tissue *relating to* the tissue's utility for reconstruction, repair, or replacement." 21 C.F.R. § 1271.3(f) (emphasis added).

23. According to FDA, "examples of HCT/Ps that we consider to be minimally manipulated include those that have been subjected to the following procedures:…cutting, grinding, or shaping." 66 Fed. Reg. at 5457. For instance, FDA characterized bone allografts as minimally manipulated. "We consider cutting, shaping and grinding of bone minimal manipulation. Threading and other machining procedures that are performed to create bone dowels, screws, and pins are also considered minimal manipulation." *Id*.

24. The HCT/P regulations define "**Homologous use**" as "the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor." 21 C.F.R. § 1271.3(c).

[1] The two other criteria that must be met under the regulations require that: (i) the HCT/P is not combined with a regulated drug or device (with a few exceptions); and (ii) the HCT/P does not have a systemic effect and it is not dependent upon metabolic activity of living cells for its primary function, and is for autologous use, allogeneic use in a first-degree or second degree blood relative, or reproductive use. 21 C.F.R. § 1271.10(a)(3)-(4). FDA did not base its decision in this matter on either of these two criteria.

25. In determining whether an HCT/P product is intended for homologous or nonhomologous use, FDA focuses on the "objective intent of the HCT/P's manufacturer for nonhomologous use, rather than on the intent of the practitioner who uses the HCT/P." In other words, FDA considers whether the product was "advertised, labeled, or otherwise objectively intended by the manufacturer for a nonhomologous use." 66 Fed. Reg. at 5458-59.

26. FDA also clarified that the "use of a structural tissue may be homologous even when it does not occur in the same location as it occurred in the donor." 66 Fed. Reg. at 5458. For example, the "use of bone for repair, replacement, or reconstruction anywhere in the skeleton of the recipient…would be considered homologous use." FDA interprets the term "'nonhomologous' narrowly." *Id* at 5458.

FDA's HCT/P 2020 Guidance and Prior Statements

27. In July 2020, FDA published guidance that further provides FDA's interpretation of the "minimally manipulated" and "intended for homologous use only" requirements, titled *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use* (the "2020 Guidance").[2]

28. The 2020 Guidance (pg. 1) replaced similar guidance with the same title that was published in November 2017 and updated in December 2017 ("2017 Guidance").[3]

29. As to **HCT/Ps** generally, FDA states that they "may perform multiple functions and FDA acknowledges that structural tissues contain cells". Specifically, FDA says "structural [HCT/P] tissues" are those that "physically support or serve as a barrier or conduit, or connect,

[2] *See* https://www.fda.gov/media/109176/download.

[3] *See* 2017 WL 6549871.

cover, or cushion," and lists "bone" and "[a]mniotic membrane and umbilical cord" as examples. 2020 Guidance (pgs. 8-9); *see also* 2017 Guidance (pgs. 8-9).

30. FDA also notes that "[s]tructural HCT/Ps generally raise different safety and efficacy concerns than do cells or nonstructural tissues." 2020 Guidance (pg. 7) (maintaining that "many structural HCT/Ps are conventional tissues with a long established history of safe use"); *see also* 2017 Guidance (pg. 6).

31. In addressing **minimal manipulation**, "[o]riginal relevant characteristics of structural tissues generally include the properties of that tissue in the donor that contribute to the tissue's function or functions." 2020 Guidance (pg. 10); *see also* 2017 Guidance (pg. 9). FDA states that a "structural tissue characteristic is 'relevant' if it could have a meaningful bearing on the tissue's utility for reconstruction, repair, or replacement." 2020 Guidance (pg. 10). In particular, "relevant characteristics" of structural materials include "strength, flexibility, cushioning, covering, compressibility, and response to friction and shear." *Id.*

32. As to "processing," the 2020 Guidance (pg. 10) recognizes that structural tissues may be minimally manipulated "by various machining and other mechanical methods to change the size or shape of the HCT/P" provided they do not "alter[] the original relevant characteristics of the structural tissue relating to its utility for reconstruction, repair, or replacement." *See also* 2017 Guidance (pg. 9). "Processing" includes "cutting, grinding, [and] shaping." 2020 Guidance (pg. 8); *see also* 2017 Guidance (pg. 7).

33. As an example, FDA states that original relevant characteristics of "bone relating to its utility to support the body and protect internal structures include strength, and resistance to compression." 2020 Guidance (pg. 10). FDA then concludes that "[m]illing, grinding, and other methods for shaping and sizing bone may generally be considered minimal manipulation when

they do not alter bone's original relevant characteristics relating to its utility to support the body and protect internal structures." *Id.* (giving example of a manufacturer who grinds bone to form chips and particles); *see also* 2017 Guidance (pg. 9).

34. As another example, FDA states the "[o]riginal relevant characteristics of amniotic membrane relating to its utility to serve as a barrier generally include the tissue's physical integrity, tensile strength, and elasticity." 2020 Guidance (pg. 11). Where amniotic membrane is preserved and packaged in sheets, it "generally is considered minimally manipulated because the processing does not alter the original relevant characteristics…relating to its utility to serve as a barrier." *Id.*; *see also* 2017 Guidance (pg. 10).

35. The 2020 Guidance (pg. 12) also notes that "separation of structural tissue into components in which the original relevant characteristics relating to the tissue's utility for reconstruction, repair, or replacement are not altered generally would be considered minimal manipulation." *See also* 2017 Guidance (pg. 11).

36. Along these lines, FDA concludes that "extraction or separation of cells from structural tissue in which the remaining structural tissue's original relevant characteristics relating to its utility for reconstruction, repair, or replacement remain unchanged generally would be considered minimal manipulation." 2020 Guidance (pg. 12); *see also* 2017 Guidance (pg. 11). For instance, a "manufacturer processes amniotic tissue to remove the chorion and other cells. The HCT/P generally is considered minimally manipulated because the processing does not alter the original relevant characteristics of the HCT/P relating to its utility to serve as a barrier." 2020 Guidance (pg. 12); *see also* 2017 Guidance (pg. 11).

37. FDA also previously published a document titled *Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Product List* in which FDA excludes

"preserved umbilical cord veins" from the category of Section 361 HCT/Ps, which as explained below is the conduit material that Vitti Labs removes from the umbilical cords, thus leaving tissue material that serves as a barrier, cover, or cushion.

38. When discussing **homologous use**, the 2020 Guidance (pgs. 16-17) includes HCT/Ps "that may not be identical to the donor's…tissues, but that perform one or more of the same basic functions in the recipient as the…tissues performed in the donor…It is not necessary for the HCT/P in the recipient to perform all of the basic functions it performed in the donor in order to meet the definition of homologous use." *See also* 2017 Guidance (pgs. 15-16).

39. FDA says that "basic" means the "function or functions that are commonly attributed to the HCT/P as it exists in the donor. Basic functions are well understood; it should not be necessary to perform laboratory, pre-clinical, or clinical studies to demonstrate a basic function or functions for purposes of applying the HCT/P regulatory framework." 2020 Guidance (pg. 17); *see also* 2017 Guidance (pg. 16).

40. According to the 2020 Guidance (pg. 18), "[b]asic functions of structural tissue would generally be to perform a structural function, for example, to physically support or serve as a barrier or conduit, or connect, cover, or cushion." *See also* 2017 Guidance (pg. 17).

41. In contrast, the "basic functions of a vein or artery include serving as a conduit for blood flow throughout the body." 2020 Guidance (pg. 18); *see also* 2017 Guidance (pg. 17).

42. Moreover, the HCT/P does not have to be used in the same anatomic location in the recipient to perform the same basic function or functions seen in the donor. "A transplanted HCT/P could replace missing tissue, or repair, reconstruct, or supplement tissue that is missing or damaged, either when placed in the same or different anatomic location." 2020 Guidance (pg. 20); *see also* 2017 Guidance (pg. 19).

43. By way of example, FDA notes the "basic functions of amniotic membrane [from the placenta] include serving as a selective barrier for the movement of nutrients between the external and in utero environment, protecting the fetus from the surrounding maternal environment, and serving as a covering to enclose the fetus and retain fluid in utero." Where amniotic membrane is applied to the surface of an eye to cover or offer protection from the surrounding environment during ocular repair and reconstruction procedures, this is "homologous use because serving as a covering and offering protection from the surrounding environment are basic functions of amniotic membrane." 2020 Guidance (pg. 19); *see also* 2017 Guidance (pg. 18).

44. As another example, FDA cites to allogeneic mineralized or demineralized cortical human bone ("DBM") used to fill bony voids or gaps. This would be a homologous use in all locations provided it is supplementing the recipient's bone for support or protecting internal structures. 2020 Guidance (pg. 21); *see also* 2017 Guidance (pg. 20).

45. Finally, according to the 2020 Guidance (pg. 21), when determining a manufacturer's intended use of the product, the HCT/P's labeling and advertising, as well as other public statements made by the manufacturer, may only refer to homologous uses for the HCT/P to qualify for regulation solely under Section 361. *See also* 2017 Guidance (pg. 20).

46. FDA's "Good guidance practices" provide that FDA employees may only depart from a guidance document with "appropriate justification." 21 C.F.R. § 10.115(d)(3).

Vitti Labs

47. Vitti Labs is a tissue bank that was founded in 2018 and began production in 2019. The company's founder, Phillip Vitti, relied on FDA's policies in place at the time and

invested significant amounts of his own money to create tissue-based products used by physicians to positively impact their patients' lives.

48. Vitti Labs designed its facility and products around the Section 361 framework and implementing regulations. The company's marketing and testing processes, quality management system, labeling and packaging, and supply and distribution chains, among other aspects of its business, were tailored to ensure that its products qualify under Section 361, and in doing so Vitti Labs reasonably relied on the HCT/P regulations and FDA guidance.

49. From the onset, Vitti Labs has been registered with FDA as a Section 361 HCT/P manufacturer.

50. Vitti Labs is also accredited by the American Association of Tissue Banks ("AATB") and, as part of that accreditation process, has passed AATB's rigorous inspection criteria as a Section 361 HCT/P producer in compliance with Current Good Tissue Practice ("CGTP"). AATB is a professional, non-profit, scientific, and educational organization that is the only national tissue banking organization in the U.S. In fact, FDA cites AATB's "Standards for Tissue Banking" in its Compliance Program Guidance Manual (CPGM) 7341.0002 entitled *Inspection of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)*.

51. AATB's Accreditation Policies make clear that only "tissue establishments that provide human tissue for transplantation or transfer" may be accredited. In other words, manufacturers of drug biologics would not qualify for accreditation.

52. Vitti Labs has successfully completed five extensive AATB audits, most recently in June 2024.

53. Vitti Labs has also implemented a comprehensive Quality Management System ("QMS") and Standard Operating Procedures ("SOPs") to ensure compliance with the Section 361 regulations.

54. Human tissues, much like organ transplantation, are in limited supply. FDA implemented a tiered risk-based approach in 2005 under Section 361 of the PHS Act to provide the public with more access to these tissues while maintaining strict regulations and guidelines to protect the public from communicable disease and microbial contamination. Human tissue products are not based on technical designs like medical devices or formulations like drugs. Because of the unique nature of processing human tissue into clean and manageable sizes for transplantation, without Section 361, human tissues would not be able to otherwise satisfy regulatory standards for drugs and devices. Due to this section, over 2.5 million tissue transplants are performed each year in the U.S. *See* https://donatelife.net/donation/organs/tissue-donation/.

CORDGRAFT Product

55. Vitti Labs produces products made from bio-ethically donated umbilical cords from Caesarian section ("C-section") births following full-term pregnancies.

56. The subject of this Complaint is CORDGRAFT, a banked human structural umbilical cord tissue product intended to be regulated under Section 361 of the PHS Act and serve as a barrier, cover, or cushion. It is not presently in commercial distribution, but Vitti Labs is preparing to launch it in the near future, subject to confirmation of its regulatory status.

57. CORDGRAFT consists solely of the umbilical cord tissue that remains after the two arteries and vein have been physically removed from the organ by manual separation techniques (discussed below). The remaining non-conduit umbilical cord tissue's anatomical name is Wharton's jelly (*substantia gelatinea funiculi umbilicalis*).

58. Wharton's jelly is the gelatinous extracellular matrix contained within the umbilical cord that protects the umbilical vessels. It prevents the conduits from compressing and provides flexibility to allow for fetal movement within the amniotic cavity. The main function of the umbilical cord is to house and protect the umbilical vessels so the fetus can move and turn without compression of its blood supply.

59. The umbilical cords are obtained from C-section births from appropriately consented, screened, healthy donors from a Tissue Recovery Organization that has been selected and qualified by Vitti Labs Quality Assurance, preferably accredited by AATB, duly registered and listed with FDA, and that complies with FDA's CGTPs.

60. The birth mother will have been appropriately screened for risk factors of relevant communicable diseases utilizing the AATB standardized Donor Risk Assessment Interview ("DRAI"). The birth mother's blood is also tested and must be found to be not-reactive for numerous communicable diseases (e.g., HIV I/II). This testing is performed by an accredited infectious disease testing laboratory (accredited under the Clinical Laboratory Improvement Amendments of 1988). 42 U.S.C. § 263(a).

61. CORDGRAFT processing consists entirely of mechanical/physical steps to clean the tissue, cut out the conduit structures (arteries and vein), cut the remaining non-conduit tissue into standard size sheets to make them manageable for the clinician to handle, and freeze the sheets for packaging and distribution. There are no changes to the chemical or biological composition of the material. For example, no effort is made to preserve live cells in the tissue because their presence or absence is not relevant to the barrier, cover, and/or cushion effects that CORDGRAFT provides.

62. Specifically, the umbilical cord is placed in a tray and cut lengthwise to expose the arteries and vein. The conduit material is then carefully removed using forceps and a scalpel (if needed). Any blood and blood clots are then rinsed away using a needle syringe. This process is solely for cleaning the surface of the tissue and does not serve any other function (e.g., decellularization). The remaining tissue is then cut into 1.5x1.5 cm or 2.5x2.5 cm sheets. The sheets are placed in a tube with saline and into a cryo freezer (-80° F) for distribution.

63. Vitti Labs intends to preserve the original relevant characteristics of the umbilical cord by employing methods that do not change its basic functions or characteristics to serve as a barrier, cover, or cushion. Vitti Labs' only intent is to simply shape and size the tissue to facilitate transplantation and ease of handling by physicians. Along these lines, no processing methods have been implemented to preserve the cells or cellular components of the tissue.

64. CORDGRAFT is also intended by Vitti Labs for homologous use as a barrier, cover, or cushion for use during surgical procedures to cover exposed structures such as nerves and tendons.

Vitti Labs' Request for Confirmation

65. On February 28, 2023, in accordance with guidance provided on FDA's webpage, Vitti Labs submitted a Request for Confirmation of Products as Regulated Solely Under Section 361 of the PHS Act. Ex. A. This was an informal request to FDA's Tissue Reference Group ("TRG"), which provides a single reference point for product specific questions concerning, *inter alia*, whether a product qualifies for regulation as an HCT/P exclusively under Section 361.

66. In the correspondence, Vitti Labs specifically set forth grounds for finding that the tissue is only minimally manipulated and is intended for homologous use. Ex. A at 3-9. Vitti Labs outlined: (i) the source of the products (i.e., bio-ethically donated umbilical cords from C-

sections); (ii) each processing step (e.g., cutting the umbilical cord lengthwise, rinsing and removing the arteries and vein, shaping the tissue into smaller sheets, and freezing the sheets before packaging and distribution); and (iii) CORDGRAFT's intended use to provide cushioning and support functions in various areas of the body, like soft tissue and joints.

67. On June 22, 2023, FDA responded in a two-page letter with virtually no analysis or discussion. Ex. B. Instead, in conclusory fashion, FDA stated that CORDGRAFT is not minimally manipulated because the "processing appears to alter the original relevant characteristics of the tissue relating to its utility to act as a conduit and therefore your CORDGRAFT product appears to be more than minimally manipulated." Ex. B at 1.

68. There was no mention of an umbilical cord's other functions, including serving as a barrier, cushion, or cover. Nor was there any acknowledgment of the regulatory definition of "minimal manipulation" (21 C.F.R. § 1271.3(f)(1)) and guidance issued by FDA that, *inter alia*: (i) focus on relevant characteristics of the tissue relating to its utility for reconstruction, repair, or replacement in the recipient; (ii) permit structural tissue to be separated into components, including those going to its utility for reconstruction, repair, or replacement in the recipient; and (iii) allow structural tissue to undergo processing (e.g., cutting) to change its size and shape. *See* Ex. A at 6-7 (Vitti Labs discussing HCT/P regulations and guidance).

69. FDA's response also did not address homologous use or rely on Section 361 criteria other than minimal manipulation for support. FDA stated the recommendation "does not represent an analysis of all the criteria specified in § 1271.10(a)." Ex. B. at 1.

70. FDA then stated if Vitti Labs disagreed with the recommendation, it could submit a Request for Designation ("RFD") to obtain a formal, binding determination on CORDGRAFT's classification (i.e., as a Section 361 product only, or as a drug or biologic). Ex.

B at 2. A classification made in response to an RFD cannot be changed "except with the written consent of the [submitter], or for public health reasons based on scientific evidence." 21 U.S.C. § 360bbb-2(b); 21 C.F.R. § 3.9.

Vitti Labs' Request for Designation

71. On July 16, 2024, pursuant to 21 U.S.C. § 360bbb-2 and 21 C.F.R. § 3.7, Vitti Labs submitted an RFD to FDA for the CORDGRAFT product. Ex. C. This was a formal request for FDA to designate CORDGRAFT as regulated solely under Section 361. Within 60 days, FDA was required to classify the product as regulated as a Section 361 product only, or under more burdensome provisions as a drug or biologic.

72. In the RFD, Vitti Labs demonstrated CORDGRAFT meets all of the criteria in 21 C.F.R. § 1271.10(a) and thus is an HCT/P regulated solely under Section 361.

73. First, Vitti Labs explained that the umbilical cord and CORDGRAFT qualify as an **HCT/P**. The umbilical cord consists of tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. 21 C.F.R. 1271.3(d)(2); Ex. C at 1. Current FDA guidance also specifically identifies umbilical cord as an example of a structural tissue that "physically support[s] or serve[s] as a barrier or conduit, or connect, cover, or cushion." *See*, *e.g.*, 2020 Guidance (pgs. 8-9). Even though the arteries and vein (i.e., conduits) are removed from the umbilical cord, the remaining material (Wharton's jelly) still serves as a barrier, cushion, or cover. Ex. C at 3-4, 7, 13.

74. Second, Vitti Labs demonstrated that the umbilical cord is only **minimally manipulated**. An original relevant characteristic of the tissue is its ability to serve as a barrier, cover, or cushion. The scientific literature contains descriptions of the long-known and well-

understood protective and cushioning elements of the umbilical cord (primarily Wharton's jelly) and how they impact the separate, conductive parts of the cord. Ex. C at 4, 8-9.

75. For example, Heil, J.R., et al., *Embryology, Umbilical Cord*, National Library of Medicine (last updated April 17, 2023), stated "Wharton's jelly is the gelatinous extracellular matrix contained within the umbilical cord that serves as protection for the umbilical vessels. It prevents the umbilical cord from compressing and provides flexibility to allow for fetal movement within the amniotic cavity…Wharton's jelly protects the umbilical vessels so the fetus can move and turn without compression of its blood supply…Wharton's jelly, the gelatin-like extracellular matrix surrounding the umbilical vessels, provides anelastic cushioning resistant to compression and twisting, allowing for continued flow with fetal movement." Ex. C at 8.

76. Similarly, Spurway, J., et al., *The development, structure and blood flow within the umbilical cord with particular reference to the venous system*, Australasian Journal of Ultrasound in Medicine, 15:97-102 (2012), stated that Wharton's Jelly "is a mucous connective tissue surrounding the umbilical vessels…The fully developed umbilical cord normally contains two umbilical arteries, one umbilical vein, the remnant of the allantois all embedded in Wharton's jelly and surrounded by a single layer of amnion." Ex. C at 8.

77. Accordingly, Vitti Labs demonstrated that the umbilical cord is a multi-tissue, multi-function organ, and acting as a conduit is only one of its functions. In fact, as noted above, FDA guidance refers to the "vein" and "arteries" in an umbilical cord, not the umbilical cord as a whole, as serving the conduit function. Other components of the cord (principally, the Wharton's jelly) provide structure, cushioning, and protection, precisely the "original relevant characteristics" of structural material as described in the HCT/P regulations and FDA guidance. *See*, *e.g.*, 2020 Guidance (pg. 10); Ex. C at 4, 9.

78. Vitti Labs also noted that just because the conduit material is removed does not change this conclusion. As FDA stated in guidance, separating structural tissue into components is minimal manipulation provided the tissue's utility for reconstruction, repair, or replacement is not altered. *See*, *e.g.*, 2020 Guidance (pg. 12). Just as separating cells from amniotic membrane is minimal manipulation, there is no principled reason to view an umbilical cord with the conduit material removed any differently because such processing does not alter the tissue's ability to serve as a barrier, cushion, or cover. *See*, *e.g.*, 2020 Guidance (pg. 12); Ex. C at 9.

79. Moreover, Vitti Labs demonstrated that processing through limited mechanical/physical means is also consistent with minimal manipulation. After the umbilical cord is cut lengthwise and the two arteries and vein are removed, the umbilical cord is simply cut into small sheets which retain their original relevant characteristics as a barrier, cover, or cushion. Cutting the umbilical cord does not change its biological composition or otherwise increase any risk to a patient. The HCT/P regulations and FDA guidance make clear that shaping and sizing of a tissue through cutting is minimal manipulation. There is no material distinction between this and manufacturing bone allografts or amniotic membrane sheets. *See*, *e.g.*, 66 Fed. Reg. at 5457; 2020 Guidance (pgs. 8-11); Ex. C at 6, 13-14.

80. Third, Vitti Labs explained that CORDGRAFT is also intended for **homologous use**. As described by FDA, one of the "basic" functions of structural material is to serve as a barrier, cover, or cushion, just as CORDGRAFT does during surgical procedures. *See*, *e.g.*, 2020 Guidance (pg. 18). Indeed, research commonly attributes such basic functions to Wharton's jelly in the umbilical cord. It is not necessary that CORDGRAFT also serve as a conduit in the recipient to be a homologous use. *See*, *e.g.*, 2020 Guidance (pgs. 16-17); Ex. C at 8, 14. To a large extent, homologous use is intertwined with minimal manipulation since the "original

relevant characteristics" of an HCT/P in the donor are directly tied to its "basic function or functions in the recipient."

81. Further, as Vitti Labs pointed out, it is irrelevant that a structural material like CORDGRAFT will be used in different locations in a recipient. Just as it is a homologous use to apply amniotic membrane from the placenta as an eye covering, or bone from one part of a donor's skeleton to fill bony gaps in other parts of a recipient, the same holds true when CORDGRAFT is used to cover, cushion, and protect exposed structures during surgery. *See*, *e.g.*, 66 Fed. Reg. at 5458; 2020 Guidance (pgs. 19, 21); Ex. C at 14.

82. Vitti Labs also noted in the RFD that it does not make any claims for CORDGRAFT related to the diagnosis, mitigation, treatment, or prevention of any condition or disease. Ex. C at 14.

83. As summarized in the RFD, CORDGRAFT provides cushioning and support functions that healthcare professionals find useful in various areas of the body (e.g., soft tissue and joints). This activity is clearly "homologous use" because the tissue is providing the "same basic function," just in a different part of the body. Ex. C at 14.

84. Finally, Vitti Labs stated that CORDGRAFT is similar to numerous other umbilical cord sheet products that are marketed as Section 361 HCT/Ps and have been available for many years. As an example, the RFD cited to Smith & Nephew's "Stravix" line of umbilical cord tissue products (and included an image). Similar to CORDGRAFT, Stravix is derived from umbilical tissue and is available in sheets of differing sizes (e.g., 2x2 cm). It is intended for homologous use as a cover/wrap/barrier and may be used for acute and chronic wounds. Stravix's producer (a subsidiary of Smith and Nephew) is registered with FDA as a Section 361 HCT/P manufacturer and lists the Stravix line as HCT/P products. Ex. C at 11-13.

85. As indicated in the RFD: (i) in 2013, FDA informed Smith & Nephew that two of its tissue products (which were marketed before Stravix) did not satisfy the Section 361 criteria; (ii) in 2015, Smith & Nephew introduced the Stravix products to the marketplace; and (iii) in 2016, FDA conducted an inspection of Smith & Nephew's facility without questioning the Section 361 status of the Stravix products. Ex. C at 11-13. FDA has conducted multiple FDA inspections of Smith & Nephew facilities since that time without raising concerns about the regulatory status of Stravix. By treating Stravix and CORDGRAFT differently, FDA violates a fundamental principle of administrative law that similarly situated entities must be regulated in the same manner.

86. Vitti Labs concluded the RFD by recommending that CORDGRAFT be designated as a Section 361 product and exclusively regulated under that section.[4] Ex. C at 15.

FDA's Response to the RFD

87. On September 20, 2024, FDA responded to Vitti Lab's RFD. Ex. D. FDA stated that "[w]e disagree with your recommendation that your product is an HCT/P regulated solely under section 361 of the PHS Act and the regulations in 21 CFR part 1271. We have determined that CORDGRAFT is an HCT/P regulated under section 351 of the PHS Act as a biological product." Ex. D at 2; *see also id.* at 1, 6, 9.

88. Like its response to Vitti Lab's Request for Confirmation, FDA's conclusion was based on only one of the four criteria at 21 C.F.R. § 1271.10(a), namely that CORDGRAFT is allegedly "more than minimally manipulated." Ex. D at 3. In a footnote, FDA "note[d] that your

[4] The RFD also demonstrated that CORDGRAFT satisfies the remaining two criteria for regulations solely under Section 361 as it is not combined with a drug or device, nor does it have a systemic effect or depend upon the metabolic activity of living cells for its primary function. 21 C.F.R. § 1271.10(a)(3)-(4); Ex. C at 15.

product also may not meet other criteria in 1271.10(a), including, for example, 1271.10(a)(2) or (a)(4).” But FDA ultimately found that it was “not necessary to address other criteria described in 1271.10(a), including, for example, 1271.10(a)(2) or (a)(4).” Ex. D at 6 n.10.

89. As to minimal manipulation, FDA maintained that the “starting point” for determining the “original relevant characteristics” of the HCT/P was the umbilical cord “as a whole.” Ex. D at 3, 5. According to FDA, there is only one “basic function” of an umbilical cord and that is to serve “[i]n the donor (before removal)” as a “conduit for unimpeded blood flow between the mother and fetus.” Ex. D at 3 n.3. “All the components of the cord, including the umbilical blood vessels, the umbilical connective tissue, and the umbilical epithelial layer, work together in a coordinated fashion to perform this role.” Ex. D at 3.

90. FDA recognized that Wharton’s jelly protects against the “compressions and torsional strains due to fetal movements.” Yet FDA argued that this was possible due to the “tubular structure of the umbilical epithelial layer and connective tissue,” which is “critical to maintain unimpeded blood flow.” Ex. D at 4-5 (maintaining that all parts of the umbilical cord function as “one unit” and “as a whole”).

91. FDA then concluded Vitti Labs more than minimally manipulates the umbilical cord when it cuts the tissue longitudinally so that it no longer is in a tubular form. FDA argued that, at this point, the tissue lost its utility for reconstruction, repair, or replacement. In doing so, FDA disagreed that umbilical cord functions as a cover, cushion, or barrier, and instead reiterated its position that the cord only serves as a “conduit” for blood flow. Ex. D at 4; *see also id.* at 5 (claiming the “appropriate departure point” for determining the tissue’s original relevant characteristics is the entire umbilical cord).

92. Significantly, FDA made clear that its determination regarding minimal manipulation was not based on the fact that the arteries and vein are removed or that the tissue is cut into standard sized sheets. As such, FDA's response is based solely on Vitti Labs' longitudinal slicing of the umbilical cord. Ex. D at 5 n.6.

93. Moreover, FDA again ignored its prior statements without explanation. FDA previously indicated that umbilical cords are structural tissues that have multiple functions, such as serving as a barrier, cover, or cushion. *See*, *e.g.*, 2020 Guidance (pgs. 8-9). FDA's response to the RFD therefore directly contradicted FDA's previous description of umbilical cords; FDA never stated that umbilical cords only serve as conduit material. In fact, when specifically discussing "conduit" material, FDA has referred to veins and arteries as an example, not an umbilical cord as a whole. 2020 Guidance (pg. 18). FDA guidance also noted that a relevant characteristic of structural material supporting its utility for reconstruction, repair, or replacement is providing cushioning, covering, and compressibility. *See*, *e.g.*, 2020 Guidance (pg. 10). FDA's response contravenes this position as well. Further, FDA has stated that structural tissues maintain their relevant functions as a barrier, cover, or cushion even after being shaped and cut. *See*, *e.g.*, 2020 Guidance (pg. 10). For instance, FDA previously maintained in guidance that whole bone provides structural "support," including "strength…and resistance to compression." *Id*. But FDA never explained how manufacturing bone chips or particles out of whole bone, which is often in tubular or three-dimensional form in the donor, is minimal manipulation, but that one longitudinal cut means the umbilical tissue ceases entirely to provide any benefits as a barrier, cushion, or cover. *See*, *e.g.*, 2020 Guidance (pg. 11). FDA also failed to recognize that Vitti Labs intends for practitioners to use the sheets to "wrap exposed structures such as nerves and tendons" during surgery, which is effectively a "tubular" form. Ex. C at 11.

94. Further, FDA mischaracterized the RFD. Contrary to FDA's claims, Vitti Labs never said that the appropriate starting or departure point for the minimal manipulation analysis is the Wharton's jelly after processing. *See* Ex. D at 5. Rather, Vitti Labs acknowledged, consistent with FDA guidance, that the relevant function for reconstruction, repair, or replacement is based on the umbilical cord. *See*, *e.g.*, Ex. C at 9 (noting that the umbilical cord is a "multi-tissue, multi-function organ, and acting as a conduit is only one of its functions"). This is entirely consistent with FDA's view that an "umbilical cord" and other structural tissues serve as a barrier, cushion, or cover. *See* 2020 Guidance (pgs. 8-9).

95. FDA also rejected Vitti Labs' suggestion that the marketing of the Stravix line of umbilical cord sheet products is an appropriate comparison. FDA complained that it did not have enough information regarding how the Stravix products are processed and noted that it had not formally classified them as regulated solely under Section 361. Ex. D at 6 n.9. But FDA failed to acknowledge the fact that manufacturers do not need to obtain a formal classification from FDA to sell tissue products that satisfy the Section 361 factors, or that Stravix is sold in sheets, which clearly indicates that the umbilical cord was cut lengthwise so that it lost its tubular shape, the only basis for FDA's finding that CORDGRAFT is more than minimally manipulated.

96. Finally, FDA stated that "CORDGRAFT is appropriately classified as a biological product" under Section 351 of the PHS Act. Ex. D at 6. A "biological product" means "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product…applicable to the prevention, treatment, or cure of a disease or condition in human beings." Ex. D at 6 n.11.

97. FDA argued that CORDGRAT (i.e., Wharton's jelly) likely contains proteins and other cells that would have therapeutic benefits (e.g., skin wound healing) when placed on

exposed structures during surgery. Ex. D at 7 n.14; *id.* at 8 n.18. In other words, FDA speculated that the "primary intended purpose of your product is to protect exposed bodily structures in surgical procedures…through chemical action within or on the body." Ex. D at 7-8. FDA did not, however, cite any statements made by Vitti Labs indicating such intent. Rather, FDA egregiously mischaracterized Vitti Labs' use of the terms "protection" or "protect" to imply that Vitti Labs intended CORDGRAT to serve as something other than physical protection (i.e., barrier, cover, or cushion). Ex. D at 7-8. Vitti Labs made clear in its Request for Confirmation and RFD that it intends for CORDGRAFT to provide protection through physical means and expressly disclaimed any intent for the CORDGRAFT to cure, mitigate, treat, or prevent any condition or disease. *See*, *e.g.*, Ex. A at 7-8; Ex. C at 8.

Vitti Labs' Request for Reconsideration

98. On October 4, 2024, pursuant to 21 C.F.R. § 3.8(c), Vitti Labs submitted a Request for Reconsideration ("RFR") to FDA. Ex. E. As FDA's regulation limits such request to just five pages, Vitti Labs expressly stated that it did not waive any other arguments not appearing in the RFR that may otherwise apply. Ex. E at 1 n.1.

99. In the RFR, Vitti Labs explained that FDA's response to the RFD based solely on the minimally manipulated factor should be reconsidered for two primary reasons.

100. First, FDA's focus on the umbilical cord as a single entity improperly disregarded the multiple, unique tissue components that compose the larger organ. Vitti Labs pointed out that this approach violates the plain language of the HCT/P regulation and/or does not represent a reasonable interpretation of those provisions. "Minimal manipulation" is defined to mean "processing that does not alter the original *relevant* characteristics of the tissue *relating to* the tissue's utility for reconstruction, repair, or replacement." 21 C.F.R. § 1271.3(f)(1) (emphasis

added). Accordingly, FDA read out of the definition the point that it is the "relevant" characteristics of the tissue that matter and, specifically, those that "relat[e] to" its ability to aid "reconstruction, repair, and replacement." There is no indication that the minimal manipulation analysis is limited to the organ's function in the donor as a whole. Ex. E at 3. Indeed, the phrase "utility for reconstruction, repair, or replacement" clearly refers to the function in the recipient, and thus that is the relevant characteristic that must be preserved following any processing.

101. This point is clearly illustrated by additional language in the HCT/P regulations. As discussed by Vitti Labs, an HCT/P is defined to include "human tissue" like a "heart valve" or "cornea." 21 C.F.R. § 1271.3(d)(2). Significantly, both tissues are part of a larger organ (heart or eye), but both can also be evaluated on their own merits under the Section 361 framework based on the functions they provide. For instance, in the 2020 Guidance (pg. 18), FDA notes that the "basic functions of the cornea include protecting the eye and serving as its outermost lens." This means that a donor's cornea can be regulated exclusively under Section 361 based on the function (protection) that the cornea provides to the larger organ. *Id.* However, by FDA's reasoning set forth in the RFD response, the cornea cannot be regulated solely under Section 361 because it is an integrated part of the overall eye. Ex. E at 2.

102. In the RFR, Vitti Labs also reiterated that the umbilical cord is a multi-tissue, multi-function organ. The umbilical cord's components serve more than one function, including Wharton's jelly providing structure, cushioning, and protection. In fact, FDA's response to the RFD explicitly recognized that various components of the umbilical cord have these specific functions. Ex. E at 2. Yet FDA never explained why Wharton's jelly is materially different than components of a heart or eye as those component tissues are identified in the HCT/P regulations.

103. Second, the proper focus of the "minimal manipulation" assessment is the tissue that is being processed for use as a Section 361 HCT/P in the recipient. *See*, *e.g.*, *United States v. US Stem Cell Clinic, LLC*, 998 F.3d 1302, 1311 (11th Cir. 2021) (holding that it was the basic function of the stromal-vascular fraction (or stem cells) of the larger adipose tissue removed from the donor that was the proper benchmark for determining homologous use); *United States v. Regenerative Sciences, LLC*, 741 F.3d 1314, 1321 (D.C. Cir. 2014) (considering the relevant biological characteristics of stem cells taken from bone marrow or fluid extracted from the donor when considering the minimal manipulation factor). As Vitti Labs pointed out, FDA should have therefore similarly looked to the function of Wharton's Jelly in the entire umbilical cord, as that would provide the "relevant" characteristics that must be preserved after processing. Ex. E at 3.

104. Vitti Labs explained in the RFR that this approach is entirely consistent with the HCT/P regulations and FDA guidance discussing the minimal manipulation criteria. For example, the 2020 Guidance (pg. 10) notes that the original relevant characteristics of bone include providing support for the body and protection for internal structures through strength and resistance to compression. FDA then states that demineralized bone matrix ("DBM") produced through milling, grinding, and other methods for shaping and sizing the bone, including forming bone chips and particles, constitutes minimal manipulation. As Vitti Labs pointed out, the guidance reflects a clear focus on the relevant properties of the processed tissue in the recipient, rather than the donor. DBM does not exist in the donor. Yet FDA did not explain how its characterization of DBM is unique and would not equally apply to umbilical cord tissue undergoing minimal processing. Ex. E at 4. While FDA argued that Vitti Labs' processing means that the umbilical cord losses its tubular shape, the same holds true when a whole bone is manufactured into DBM. As such, FDA did not adequately explain how the remaining materials

making up CORDGRAFT cease to retain their original relevant characteristics as a barrier, cushion, or cover. Ex. E at 3.

105. Vitti Labs' RFR is also consistent with the regulatory definition of "HCT/P." That term is defined as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient." 21 C.F.R. § 1271.3(d)(2). Clearly, there would be few (if any) circumstances where an umbilical cord as a whole would be "intended for implantation, transplantation, infusion, or transfer into a human recipient." Instead, it is a component of the umbilical cord (in the form of CORDGRAFT containing Wharton's jelly) that is transferred into the recipient.

106. As also noted in the RFR, FDA did not justify its differential treatment of products similar to CORDGRAFT, such as Stravix (or DBM). For example, while FDA complained in conclusory fashion that it did not have sufficient information regarding Stravix and that it had not classified the product as being regulated solely under Section 361, Vitti Labs explained that Stravix's manufacturer is not required under the regulations to seek any designation. Moreover, the availability of a product for eight years, prominently marketed as a section 361 HCT/P by a high-profile medical products company without objection from FDA, warrants its consideration as a comparable product. Ex. E at 5.

107. Finally, after denying CORDGRAFT Section 361 status, FDA then classified the product as a biologic because it allegedly contains proteins and other cells that would have therapeutic effect beyond any function as a barrier, cover, or cushion. However, FDA completely ignored the fact that Vitti Labs expressly stated it does not make any effort to preserve cells and that the company therefore does not intend for CORDGRAFT to have any cellular effect.

FDA's Response to the RFR

108. On October 18, 2024, FDA responded to Vitti Labs' RFR and stated that there was no basis to change its conclusions that CORDGRAFT is ineligible for regulation exclusively under Section 361 or that it should be classified as a biologic product. Ex. F at 2.

109. As to Vitti Labs' first RFR argument ("The umbilical cord includes tissues with more than one function"), FDA raised a completely new and nonsensical argument. Prior to this latest response, FDA had maintained the "starting" or "departure" point for the minimal manipulation analysis is the overall function of the larger organ in the donor, in FDA's view the umbilical cord's function as a conduit. But now FDA believes that the analysis actually begins not with the donor but with the tissue product that is received by the manufacturer prior to processing. Ex. F at 6 ("Here, you describe the processing as beginning with the umbilical cord, not any subcomponents of the umbilical cord."). That is how, according to FDA, that a heart valve or cornea, both of which are components of larger organs, can be an HCT/P for purposes of minimal manipulation. Ex. F at 5-6. For FDA, it apparently all depends on what is sent to the HCT/P manufacturer.

110. But there is nothing in the plain language of the HCT/P regulation or guidance indicating that minimal manipulation turns on such fortuitous circumstances and, indeed, FDA assumed without any support that what is received by the manufacturer in the mail has a bearing on the tissue's "relevant" characteristics "relating to" reconstruction, repair, or replacement in the recipient. FDA never explained how an upstream tissue supplier who, before shipment to the HCT/P manufacturer, separates a heart valve from a donor's heart, or a cornea from a donor's eye, is materially different than Vitti Labs processing an umbilical cord.

111. FDA then claimed that "[b]ecause the umbilical cord is right unit of analysis for minimal manipulation criterion, the functions of the umbilical cord components are beside the point." According to FDA, "[f]or structural tissue the minimal manipulation analysis relates to examining the 'original relevant characteristics of the tissue, relating to the tissue's utility for reconstruction, repair, or replacement.' The minimal manipulation analysis does not examine the characteristics of a tissue's *components.*" Ex. F at 6 (emphasis in original). This is directly contrary, however, to the plain language of the "minimal manipulation" definition at 21 C.F.R. § 1271.3(f)(1) or any reasonable interpretation of that provision. The phrases "relevant characteristics" and "relating to" clearly indicate that FDA intended for the minimal manipulation analysis to focus on components or subparts of a larger organ – namely, the tissue's distinct utility for "reconstruction, repair, or replacement." That is how a "heart valve" or "cornea" can be an HCT/P tissue for purposes of Section 361. 21 C.F.R. § 1271.3(d)(2), and why minimal manipulation does not require a manufacturer like Vitti Labs to preserve the function of a larger tissue or organ as a whole.

112. FDA's newfound position is also contravened by numerous statements made in FDA guidance, including an explicit reference to "components." For instance, the 2020 Guidance states that: (i) HCT/Ps "may perform multiple functions" and specifically cites umbilical cord as an example of structural tissue that serves as a barrier, cushion, or cover (pgs. 8-9); (ii) a "relevant characteristic" of structural tissue is providing "cushioning and covering" (pg. 10); (iii) "separation of structural tissue into *components* in which the *relevant characteristics* relating to the tissue's utility for reconstruction, repair or replacement are not altered" constitutes minimal manipulation (pg. 12) (emphasis added); and (iv) whole bone which is then sized and shaped by the tissue manufacturer into DBM or other bone chips/particles is

minimal manipulation (pg. 10). Even FDA's response to the RFR cites back to the 2020 Guidance where it states that "a structural tissue characteristic is 'relevant' if it could have a meaningful bearing on the tissue's utility for reconstruction, repair, or replacement. The structural tissue's utility for reconstruction, repair, or replacement relates to how that tissue functions in the donor." Ex. F at 6. As FDA has said time and again, structural tissues, including umbilical cords, serve these precise functions. Yet FDA failed to reconcile its response with the plain language of the HCT/P regulations and long-standing positions on minimal manipulation.

113. FDA then returned to its prior argument that, even if the correct starting point focuses on components of the umbilical cord, merely slicing the cord lengthwise nevertheless alters the tissue's utility for reconstruction, repair, or replacement. After conceding once again that Wharton's jelly serves cushioning and protective functions, FDA claimed that these are lost once the umbilical cord's tubular structure is modified. Ex. F at 6-7. But as Vitti Labs previously noted, this does not explain how DBM, which ceases to be in the tubular form of whole bone once it is processed, is only minimally manipulated and retains the bone's utility to provide support and resistance to compression. 2020 Guidance (pg. 10).

114. As to Vitti Labs' second argument ("The tissue being processed is the appropriate focus of the minimal manipulation assessment"), FDA mischaracterized Vitti Labs' RFR and, more importantly, missed the salient point. According to FDA, Vitti Labs said the "tissue being processed" is the Wharton's jelly, not the umbilical cord. Ex. F at 2 ("As you consider 'the tissue being processed' for your product to be the umbilical cord without its blood vessels, you contend that your product is minimally manipulated since 'the remaining structural tissues still retain their original relevant characteristics to serve as a barrier…, cover, or cushion'"). FDA maintains that this does not make sense, however, because the tissue which is implanted into the recipient

has already been processed. *Id.* at 3. Therefore, in FDA's mind, the umbilical cord, not the Wharton's jelly, is the proper focus of the minimal manipulation analysis, and the only function relevant to the assessment is the umbilical cord's role as a conduit. *Id.*

115. FDA continues to conflate two different concepts – what tissue is being physically processed and what functions are relevant to the minimal manipulation analysis. Vitti Labs agrees that the umbilical cord is the tissue which is processed and never stated that it is the Wharton's jelly that undergoes processing. *See*, *e.g.*, Ex. C at 6 (RFD section titled "Steps to process umbilical cords into CORDGRAFT"). Rather, Vitti Labs' point is that the minimal manipulation analysis asks if the relevant characteristics of that tissue (the umbilical cord) remain after processing. But FDA has not offered any explanation for why Vitti Labs' processing is more than "'minimal manipulation' when the remaining structural materials [i.e., the Wharton's jelly] still retain their original relevant characteristics to serve as 'a barrier…cover, or cushion.'" Ex. E at 3.

116. For the same reason, FDA also failed to distinguish *US Stem Cell Clinic.* FDA argued this decision is irrelevant because it addresses the homologous use, not the minimal manipulation, factor. Specifically, as FDA interprets the provisions, the homologous use criterion compares the tissue's function in the donor to the intended use in the recipient because a nonhomologous use in the recipient carries greater risk of a communicable disease. 21 C.F.R. § 1271.3(c). In contrast, the minimal manipulation criterion is limited to the original relevant characteristics in the donor because further processing increases such risk. 21 C.F.R. § 1271.3(f); Ex. F at 4. FDA, however, never explains why this purported distinction carries any significance.

117. In fact, this directly contradicts the plain language of the HCT/P regulations or any reasonable interpretation thereof. FDA leaves out that portion of the minimal manipulation

definition that refers to the recipient ("relating to the tissue's utility for reconstruction, repair, or replacement") 21 C.F.R. § 1271.3(f). Minimal manipulation asks if the tissue's relevant function in the donor remains after processing so that it benefits the recipient. Thus, homologous use and minimal manipulation are ultimately concerned with the same function. Indeed, 21 C.F.R. § 1271.10(a)(1)-(2), which set out the minimal manipulation and homologous use criteria, refer to the same "regulated" material – i.e., "The HCT/P." As such, in *US Stem Cell Clinic*, the court held that "the proper benchmark" for determining the relevant function of a tissue must be based on the component stromal-vascular fraction of the larger adipose tissue. 998 F.3d at 1311. That is why *US Stem Cell Clinic* applies in Vitti Labs' case – when determining what function in the donor tissue is relevant for minimal manipulation, FDA must look at the utility of the component material that will serve as a barrier, cushion, or cover in the recipient. Ex. E at 3.

118. FDA then argued again that its approach to DBM does not support Vitti Labs' RFD. FDA maintains that the original relevant characteristics of bone (strength and resistance to compression) are different than those seen in CORDGRAFT. Ex. F at 4-5. But "FDA has never explained what factors are unique to DBM that would not also apply to another Section 361 HCT/P produced from selected components of a larger tissue/organ." Ex. E at 4.

119. In a footnote, FDA also reiterated its position that Stravix is not a "comparable product" because there is no public information regarding how it is manufactured or processed. Ex. F at 4 n.7. But as Vitti Labs explained, like CORDGRAFT, the Stravix line of products are derived from umbilical cord tissue, cut into sheets, and cryopreserved. Ex. C at 11-13; Ex. E at 4-5. That necessarily means the umbilical cord's conduit material was also removed and that the cord was cut so that it no longer retained its tubular shape, the same step that FDA cites to when arguing that CORDGRAFT is not minimally manipulated. FDA did not offer any reason to

believe that the Stravix material was subject to any other processing steps that would distinguish that product from CORDGRAFT.

120. Finally, FDA complains in a footnote that Vitti Labs did not provide information to support its assertion that storing and distributing CORDGRAFT at -80° will degrade or destroy most of cells in the product. Ex. F at 4 n.6. Vitti Labs makes no claims to destroy or retain any cells, but only relies on the tissue's basic function for its intended use. FDA fails to acknowledge that Vitti Labs' human tissue processing is not required to include steps to destroy the cells in the tissue, nor make the product acellular before packaging. Rather, Vitti Labs must only implement controls to prevent the spread of communicable disease.

121. At no point when responding to Vitti Labs' Request for Confirmation, RFD, or RFR, did FDA present any evidence that CORDGRAFT or similar HCT/Ps present any safety or health concerns for recipients. FDA never explained how merely cutting the umbilical cord lengthwise increases the risk of a communicable disease.

COUNT I

Violation of APA
5 U.S.C. § 706

122. Vitti Labs reasserts and incorporates by reference each of the preceding paragraphs.

123. CORDGRAFT satisfies all Section 361 criteria as a product to be regulated solely under those provisions of the PHS Act because the processed tissue is only minimally manipulated, is intended for homologous use, is not combined with prohibited articles, and does not have a systemic effect or depend on the metabolic activity of living cells for its primary function.

124. Under the APA, this Court "shall…hold unlawful and set aside agency action, findings, and conclusions found to be (A) arbitrary, capricious, and abuse of discretion, or otherwise not in accordance with law; (B) contrary to constitutional right, power, privilege, or immunity; (C) in excess of statutory jurisdiction, authority, or limitations, or short of statutory right; (D) without observance of procedure required by law; [and] (E) unsupported by substantial evidence." 5 U.S.C. § 706.

125. FDA's final decision violates the APA because it is directly contrary to the plain language of the Section 361 provisions and/or does not represent a reasonable interpretation of such regulations. FDA's decision, *inter alia*, ignores the definition of "minimal manipulation" when it focuses on the function of the umbilical cord in the donor as a whole instead of the "relevant characteristics" of the umbilical cord and its component Wharton's jelly "relating to" their utility in the recipient for "reconstruction, repair, or replacement." FDA's approach is also arbitrary and capricious because FDA does not adequately explain its underlying rationale or its departure from long-standing positions regarding minimal manipulation, and as such also constitutes a lack of fair notice and unfair surprise.

126. FDA's final decision violates the APA because it is contrary to the plain language of the HCT/P regulations or any reasonable interpretation thereof, and is also arbitrary and capricious because FDA fails to adhere to numerous statements in the preamble to such regulations and in FDA guidance indicating, *inter alia*, that merely cutting an umbilical cord lengthwise would not alter the relevant characteristics of its component part (Wharton's jelly) to serve as a barrier, cover, or cushion in a recipient. Again, FDA fails to adequately explain its decision or its departure from well-established positions regarding minimal manipulation, and accordingly also constitutes a lack of fair notice and unfair surprise.

127. FDA's final decision also violates the APA and constitutes arbitrary and capricious decision-making because it does not consider all relevant evidence demonstrating that CORDGRAFT is eligible for regulation exclusively under Section 361 and would not otherwise qualify as a biologic product under the PHS Act.

128. FDA also acted in an arbitrary and capricious manner when it treated CORDGRAFT differently than similarly situated HCT/P products, including the Stravix products and DBM.

PRAYER FOR RELIEF

WHEREFORE, Vitti Labs respectfully requests the following relief:

a. A declaration that FDA's RFD and RFR decisions violate the APA, including FDA's designation of CORDGRAFT as a biologic product;

b. An order declaring that CORDGRAFT meets the criteria to be regulated solely under Section 361 of the PHS Act;

c. An order vacating and remanding FDA's RFD and RFR decisions;

d. An order granting Vitti Labs reasonable attorneys' fees and expenses; and

e. An award of such further relief as this Court deems appropriate.

Dated: January 7, 2025

Respectfully submitted,

/s/ Michael F. Barzee

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